K130894

5.0 510(k) Summary

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As required by 21 CFR Section 807.92(c).

Submitted by:	Cepheid 904 Caribbean Drive Sunnyvale, CA 90489 Phone number: (408) 400-8460 Fax number: (847) 510-0539
Contact:	Kerry J. Flom, Ph.D.
Date of Preparation:	March 29, 2013
Device:	
Trade name:	Xpert® MRSA/SA Blood Culture Assay
Common name:	Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (SA) from positive blood culture bottles assay.
Type of Test:	Nucleic Acid Amplification Test, DNA, Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (SA), qualitative
Regulation number/ Classification name/ Product code:	866.1640 Antimicrobial susceptibility test powder NQX
Classification Advisory Panel	Microbiology (83)
Predicate Devices Name(s):	Xpert MRSA/SA Blood Culture Assay (510(k) #K101879) BD GeneOhm™ StaphSR Assay (510(k) #K071026)

Device Description:

The Cepheid Xpert® MRSA/SA Blood Culture Assay (Xpert MRSA/SA Blood Culture Assay) is a rapid, automated DNA test for the simultaneous qualitative detection of MRSA and SA DNA directly from blood culture bottle specimens that are detected as positive for microbial growth and shown to contain Gram Positive Cocci by Gram stain. The primers and probes in the Xpert MRSA/SA Assay detect nucleic acid sequences of the staphylococcal protein A (*spa*), the gene for methicillin/oxacillin resistance (*mecA*), and staphylococcal cassette chromosome (SCC*mec*) inserted in the SA chromosomal *attB* site.

The test includes a Sample Processing Control (SPC) to control for adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR assay. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The specimen for testing with the Xpert MRSA/SA Blood Culture Assay consists of an aliquot taken from a positive blood culture bottle. Using one of the disposable fixed 50 µL volume transfer pipettes provided with the test kit, an aliquot of the positive blood culture is transferred into a single-use tube of Elution Reagent, also provided with the kit. The Elution Reagent is briefly vortexed and the entire content is transferred to the "S" chamber of the disposable fluidic cartridge (the Xpert MRSA/SA Blood Culture Assay cartridge), after which the cartridge is ready to place on the instrument.

The assay is performed on the Cepheid GeneXpert Instrument Systems, which automate and integrate sample purification, nucleic acid amplification and detection of the target sequences in simple or complex samples using real-time PCR. The systems consist of an instrument, personal computer, and preloaded software for running the tests and viewing the results. The GeneXpert Instrument Systems require the use of single-use disposable cartridges that hold the PCR reagents and host the PCR process. Because the cartridges are self-contained, cross-contamination between samples is minimized. In this platform, additional sample preparation, amplification, and real-time detection are all fully-automated and completely integrated. The Xpert MRSA/SA Blood Culture Assay performed on the GeneXpert Instrument Systems provides results in approximately 60 minutes.

The GeneXpert Instrument Systems, comprised of the GeneXpert Dx Systems and the GeneXpert Infinity Systems, have 1 to 80 randomly accessible modules, depending upon the instrument, that are each capable of performing separate sample preparation and real-time PCR tests. Each module contains a syringe drive for dispensing fluids (i.e., the syringe drive activates the plunger that works in concert with the rotary valve in the cartridge to move fluids between chambers), an ultrasonic horn for lysing cells or spores, and a proprietary I-CORE® thermocycler for performing real-time PCR and detection.

The purpose of this submission is to submit documentation to support proposed improvements to the current assay and changes to the Intended Use.

Device Intended Use:

The Cepheid® Xpert® MRSA/SA Blood Culture Assay, performed on the GeneXpert® Instrument Systems, is a qualitative *in vitro* diagnostic test intended for the detection of *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) DNA directly from positive blood cultures. The assay utilizes automated real-time polymerase chain reaction (PCR) for the amplification of MRSA/SA specific DNA targets and fluorogenic target-specific hybridization probes for the real-time detection of the amplified DNA. The assay is performed directly on positive blood culture samples from BD BACTEC™ Plus Aerobic/F, BacT/ALERT® SA (Standard Aerobic) or VersaTREK REDOX 1® (aerobic) blood culture bottles that are determined by Gram Stain as Gram Positive Cocci in Clusters (GPCC) or as Gram Positive Cocci in singles (GPC). The Xpert MRSA/SA Blood Culture Assay is indicated for use in conjunction with other laboratory tests, such as culture, and clinical data available to the clinician as an aid in the detection of MRSA/SA from positive blood cultures. Subculturing of positive blood cultures is necessary to recover organisms for susceptibility testing or for epidemiological typing. The Cepheid Xpert MRSA/SA Blood Culture Assay is not intended to monitor treatment for MRSA/SA infections.

Substantial Equivalence:

The Xpert MRSA/SA Blood Culture Assay is substantially equivalent to the BD GeneOhm™ StaphSR Assay (510(k) #K071026) and to the current Xpert MRSA/SA Blood Culture Assay (510(k) #K101879). All assays detect SA and MRSA from positive blood cultures and determine the presence of the target organisms through real-time PCR amplification and fluorogenic target-specific hybridization detection. A multi-center study was conducted to determine the performance characteristics of the device relative to the reference culture results and susceptibility testing (the current standard of care), and relative to the predicate devices. The test results showed the Xpert MRSA/SA Blood Culture Assay to be substantially equivalent to the current standard of care and the predicate devices.

Table 5.1 shows the similarities and differences between the Xpert MRSA/SA Blood Culture Assay and predicate assays.

Table 5.1
Similarities and Differences Between the Xpert MRSA/SA Blood Culture Assay and the Predicate Devices

Similarities			
	New Device	**Predicate Devices**	
Item	**Xpert MRSA/SA Blood Culture Assay**	**Current Xpert MRSA/SA Blood Culture Assay (510(k) #K101879)**	**BD GeneOhm™ StaphSR Assay (510(k) #K071026)**
Intended Use	Rapid detection of MRSA and SA	Same	Same
Indication for Use	Identification of MRSA and SA colonization	Same	Same
Specimen Type	Positive Blood Culture	Same	Same
Technological Principles	Fully-automated nucleic acid amplification (DNA); real-time PCR	Same	Same
DNA Target Sequence	Sequence incorporating the insertion site (*attB*) of Staphylococcal Cassette Chromosome *mec* (SCC*mec*) for detection of MRSA.	Same	Same

Similarities			
	New Device	**Predicate Devices**	
Item	**Xpert MRSA/SA Blood Culture Assay**	**Current Xpert MRSA/SA Blood Culture Assay (510(k) #K101879)**	**BD GeneOhm™ StaphSR Assay (510(k) #K071026)**
Clinical Comparison Results:	Xpert MRSA/SA Blood Culture Assay Performance vs. Reference Culture : **MRSA:** Positive % Agreement: 98.1% Negative % Agreement: 99.6% **SA:** Positive % Agreement: 99.6% Negative % Agreement: 99.5%	Xpert MRSA/SA Blood Culture Assay Performance vs. Reference Culture : **MRSA:** Positive % Agreement: 100.0 Negative % Agreement: 100.0 **SA:** Positive % Agreement: 100.0 Negative % Agreement: 99.4	BD GeneOhm™ StaphSR Assay Performance vs. Reference Culture methods : **MRSA:** Positive % Agreement: 100.0 Negative % Agreement: 98.2 – 100.0 **SA:** Positive % Agreement: 98.8 – 100.0 Negative % Agreement: 96.5 – 100.0 [Data obtained from the BD GeneOhm StaphSR Assay 510(k) Summary]

Differences			
	New Device	**Predicate Devices**	
Item	**Xpert MRSA/SA Blood Culture Assay**	**Current Xpert MRSA/SA Blood Culture Assay (510(k) #K101879)**	**BD GeneOhm™ StaphSR Assay (510(k) #K071026)**
Test Cartridge	Same as current Xpert assay.	Disposable single-use, multi-chambered fluidic cartridge.	Disposable single-use PCR tube
Instrument System	Cepheid GeneXpert Dx Systems and GeneXpert Infinity Systems	Cepheid GeneXpert Dx System	Cepheid SmartCycler

Differences			
	New Device	**Predicate Devices**	
Item	**Xpert MRSA/SA Blood Culture Assay**	**Current Xpert MRSA/SA Blood Culture Assay (510(k) #K101879)**	**BD GeneOhm™ StaphSR Assay (510(k) #K071026)**
Sample Preparation	Self-contained and automated after mixed specimen is added to cartridge. All other reagents are contained in the cartridge.	Self-contained and automated after mixed specimen and two single-dose reagents are added to cartridge.	Manual
Probes	Same as current Xpert assay.	TaqMan® Probes	Molecular Beacons
Internal Controls	Same as current Xpert assay.	Sample processing control (SPC) and probe check control (PCC).	One internal reagent control and external positive and negative controls required per run
DNA Target Sequence	Same as current Xpert assay.	Sequence specific to methicillin/oxacillin resistance (*mecA* gene)	N/A
Users	Same as current Xpert assay.	Operators with no clinical lab experience to experienced clinical laboratory technologists.	CLIA High Complexity Laboratory Users
DNA Target Sequence	Same as current Xpert assay.	Sequence specific to *Staphylococcus aureus* species (*spa* gene)	Sequence specific to *Staphylococcus aureus* species (*nuc* gene)
Ability to identify correctly "Empty Cassette Variants"	Same as current Xpert assay.	Yes, sequence specific to *Staphylococcus aureus* species (*mecA* gene)	No
Rapid test results	Approximately 60 minutes to result.	Approximately 50 minutes to result.	Approximately 60-75 minutes to result.

Non-Clinical Studies:

Analytical Inclusivity (Reactivity)

Two hundred fifty (250) SA strains (47 MSSA and 203 MRSA) from multiple sources were tested using the Xpert MRSA/SA Blood Culture Assay. Selections were made to represent the primary lineages with emphasis placed on the specific clonal complexes within which MRSA is predominantly observed. Lineages that contain MRSA and MSSA, as well as those that contain MSSA exclusively were included. When characterized by pulsed-field gel electrophoresis (PFGE), numerous USA types including USA100, the most common healthcare-acquired strain and USA300 and USA400, the most common community-acquired strains were also included.[1] Strains representing "Empty Cassette" variants and heterogeneous strains identified as borderline oxacillin-resistant *Staphylococcus aureus* or BORSA were also tested.

All strains were tested in triplicate using 10 µl of stationary phase cell suspension diluted 1 million-fold. Colony forming units per assay (CFU/test) were determined by plate counts in triplicate. All results were reported correctly by the Xpert MRSA/SA Blood Culture Assay, except one specimen. The Xpert MRSA/SA Blood Culture Assay incorrectly identified one (1) SA strain (LGA251) as MSSA instead of MRSA. LGA251 contains a novel *mecA* gene representing a divergent *mecA* homologue ($mecA_{LGA251}$) located in a novel staphylococcal chromosome *mec* element, designated SCC*mec* type XI. The *mecA* primers and probes in the MRSA/SA Blood Culture Assay will not detect the novel *mecA* gene in this strain due to mutations in the primer/probe binding regions. The *mecA* gene in this strain is only 70% homologous to the *mecA* gene in other known MRSA strains.

Limit of Detection

Studies were performed to determine the two-sided 95% confidence intervals for the analytical limit of detection (LoD) of SA cells and methicillin-resistant SA (MRSA) cells diluted into a blood culture matrix that can be detected by the Xpert MRSA/SA Blood Culture Assay. The matrix consisted of SA-free whole blood and MSSE (methicillin-susceptible *Staphylococcus epidermidis*) cells at 10^6 CFU/mL added to blood culture medium. The limit of detection is defined as the lowest number of colony forming units (CFU) per sample that can be reproducibly distinguished from negative samples with 95% confidence or the lowest concentration at which 19 of 20 replicates were positive.

For MRSA, 20 replicates were evaluated at each MRSA concentration tested (CFU/test) for 10 individual isolates representing SCC*mec* types I, II, III, IVa, IVd, V, VI, VII, and VIII. When characterized by pulsed-field gel electrophoresis (PFGE), USA100, the most common healthcare-acquired strain and USA400, one of the most common community-acquired strains were represented.

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[1] Cooper, J E and Feil, E J. 2006. The phylogeny of *Staphylococcus aureus* – which genes make the best intra-species markers? Microbiology **152**:1297 – 1305.

For SA, 20 replicates were evaluated at each SA concentration (CFU/test) for 3 individual SA isolates. USA types USA900 and USA1200 were represented.
Point estimates and confidence intervals were determined by probit regression using data (i.e., the number of positive results per number of replicates at each level) spanning a range of CFU/test loadings. The confidence intervals were determined using maximum likelihood estimates on the probit model parameters using the large sample variance-covariance matrix. The LoD point estimates and 95% upper and lower confidence intervals for each SA and each MRSA SCC*mec* type tested are summarized in Tables 5.2 and 5.3.

Table 5.2: LoD and 95% Confidence Intervals - SA

SA Strain ID	PFGE ID	Confirmed LoD (CFU/test) [at least 19/20 positive]	LoD Estimate (Probit Regression Analysis) (CFU/test)		
			Lower 95% CI	LoD Estimate	Upper 95% CI
102-04[a]	USA1200	100 (19/20)	60.4	74.5	101.6
29213[b]	unknown	150 (19/20)	120.1	138.2	172.7
N7129[a]	USA900	300 (19/20)	224.2	255.2	314.8

Strain Source:
[a]American Type Culture Collection (ATCC), Manassas, VA., USA
[b]Centers for Disease Control and Prevention (CDC), Atlanta, GA., USA

Table 5.3. LoD and 95% Confidence Intervals - MRSA

MRSA Strain ID	PFGE ID	Confirmed LoD (CFU/test) [at least 19/20 positive]	LoD Estimate (Probit Regression Analysis) (CFU/test)		
			Lower 95% CI	LoD Estimate	Upper 95% CI
Type I (64/4176)[a]	USA500	350 (19/20)	332.3	366.8	433.5
Type II (N315)[b]	USA100[e]	175 (19/20)	113.7	137.0	178.1
Type III (11373)[b]	unknown	225 (19/20)	191.9	222.6	273.9
Type IVa (MW2)[b]	USA400[e]	350 (19/20)	313.1	356.1	427.0
Type V (ST59)[c]	USA1000[e]	250 (19/20)	218.2	243.1	282.3
Type VI (HDE288)[d,f]	USA800[e]	250 (19/20)	222.2	246.0	385.0
Type VII (JCSC6082)[a]	unknown	300 (19/20)	264.1	288.0	347.1
Type VIII (WA MRSA-16)[c]	unknown	400 (19/20)	348.7	386.7	499.1
Type II (BK2464)[b]	USA100[g]	125 (19/20)	94.3	116.1	162.0
Type IVd (BK2529)[b,f]	USA500[g]	200 (19/20)	120.8	148.8	202.5

Strain Source:
[a]Teruyo Ito, Department of Bacteriology, School of Medicine Juntendo University, Tokyo, Japan
[b]Barry Kreiswirth, Director Public Health Research Institute (PHRI), Newark, NJ., USA
[c]Geoffrey Coombs, Department of Microbiology and Infectious Diseases, Royal Perth Hospital, Perth WA
[d]Herminia de Lancastre, Laboratory of Molecular Genetics, Instituto de Tecnologia Quimica e Biologica (ITQB), Universidade Nova de Lisboa, Oeiras, Portugal
[e]K. Bonnstetter, et al., J Clin Micro 2007, p. 141-146; L. McDougal, et al., J Clin Micro 2003, p. 5113-5120
[f]Heterogeneous oxacillin-resistant isolates
[g]Barry Kreiswirth, personal communication

The results of this study indicate that the Xpert MRSA/SA Blood Culture Assay will produce a positive SA result 95% of the time in a positive blood culture aliquot (50 µL) containing 300 CFU and a positive MRSA result 95% of the time for a positive blood culture aliquot (50 µL) containing 400 CFU.

Linearity

Not applicable, the Xpert MRSA/SA Blood Culture Assay is a qualitative assay.

Analytical Specificity (Exclusivity)

One hundred and one (101) strains were collected, quantitated, and tested using the Xpert MRSA/SA Blood Culture Assay. Of the 101 strains tested, 91 cultures were obtained from the American Type Culture Collection (ATCC), 1 was obtained from Culture Collection, University of Göteborg, Sweden (CCUG), 1 was obtained from Teruyo Ito, Juntendo University, Tokyo, Japan, 1 carbapenemase (KPC) producing *Klebsiella pneumoniae* strain was obtained from National Collection of Type Cultures (NCTC), UK and 7 strains were obtained from the Network on Antimicrobial Resistance in SA (NARSA). These strains represent species phylogenetically related to SA or those potentially encountered in the hospital environment.

The organisms tested were identified as either Gram positive (74), Gram negative (24), or yeast (3). Methicillin-sensitive, coagulase negative *Staphylococcus*, MSCoNS (27) and methicillin- resistant, coagulase negative *Staphylococcus*, MRCoNS (12) were included. The organisms were further classified as either aerobic (94) or anaerobic (7).

Three replicates of each isolate were tested at 1.7 - 3.2 McFarland units. Under the conditions of the study, all isolates were reported MRSA NEGATIVE; SA NEGATIVE; none of the isolates were detected by the Xpert MRSA/SA Blood Culture Assay. The analytical specificity was 100%.

Potentially Interfering Substances

Substances that may be present in blood cultures with potential to interfere with the Xpert MRSA/SA Blood Culture Assay were tested in the interfering substance study. Potentially interfering substances include, but are not limited to, anticoagulated whole blood with ACD, EDTA, Heparin, and Sodium Citrate, human plasma, three blood culture media bottles (Becton Dickinson BACTEC™ Plus Aerobic/F, BioMérieux BacT/ALERT SA (Standard Aerobic), and TREK Diagnostics VersaTREK REDOX1 (Aerobic), bilirubin, γ-globulin, hemoglobin, triglycerides, and sodium polyanetholesulfonate (SPS). Bilirubin, γ-globulin, hemoglobin, and triglycerides were tested at concentrations approximately one log higher than reference levels. SPS was tested at a 10 fold higher concentration than found in blood culture media. Negative samples (n=8) were tested in each substance to determine the effect on the performance of the sample processing control (SPC). Positive samples (n=8) were tested per substance with two clinical isolates each of MSSA (29213 and 102–04) and MRSA (SCC*mec* types II and III) spiked near the analytical LoD determined for each isolate. All results were compared to positive and negative buffer controls. All negative specimens were correctly reported "MRSA NEGATIVE; SA NEGATIVE" using the Xpert MRSA/SA Blood Culture Assay. None of the

potentially interfering substances had a statistically significant inhibitory effect on SPC performance in negative samples (p-value = >0.05). All of the positive MSSA specimens were correctly reported "MRSA NEGATIVE; SA POSITIVE" using the Xpert MRSA/SA Blood Culture Assay. All of the positive MRSA specimens were correctly reported "MRSA POSITIVE; SA POSITIVE" using the Xpert MRSA/SA Blood Culture Assay. None of the potentially interfering substances resulted in a Ct difference of ≥1 cycle relative to the buffer controls and no false-negative results were reported.

Clinical Studies

Clinical Comparison Study

Performance characteristics of the Xpert MRSA/SA Blood Culture Assay were determined in a multi-site prospective study at eight US institutions by comparing the Xpert MRSA/SA Blood Culture Assay with culture.

Subjects included individuals whose routine care called for blood culture testing. If the blood culture sample was positive for microbial growth and the Gram stain showed Gram positive cocci (singles or in clusters), the sample was eligible for inclusion in the clinical study, and aliquots of leftover culture material were obtained for testing by the Xpert MRSA/SA Blood Culture Assay. Culture and Gram stain procedures, and patient management continued at the sites per the standard practice. Susceptibility testing was performed in accordance with the CLSI documents M2-A11 and M100-S22. Cefoxitin disc was used as a surrogate for detecting methicillin/oxacillin resistance.

Performance of the Xpert MRSA/SA Blood Culture Assay was calculated relative to the reference culture results.

Overall Results

A total of 792 specimens were tested for MRSA and SA by Xpert MRSA/SA Blood Culture Assay and culture.

The Xpert MRSA/SA Blood Culture Assay identified 98.1% of the specimens positive for MRSA and 99.6% of the specimens negative for MRSA relative to culture.

The Xpert MRSA/SA Blood Culture Assay identified 99.6% of the specimens positive for SA and 99.5% of the specimens negative for SA relative to the reference culture method. The performance of the Xpert MRSA/SA Blood Culture Assay is summarized in Table 5.4.

Table 5.4. MRSA/SA Performance vs. Reference Culture

		Culture			
		MRSA+	SA+/MRSA-	Neg/No Growth	Total
Xpert	MRSA+	103	2	1	106
	SA+/MRSA-	2	128	2	132
	SA-	0	1	553	554
	Total	105	131	556	792
Xpert Performance	MRSA: PPA: 98.1% (103/105, 95% CI: 93.3-99.8) NPA: 99.6% (684/687, 95% CI: 98.7-99.9)				
	SA: PPA: 99.6% (235/236, 95% CI: 97.7-99.9) NPA: 99.5% (553/556, 95% CI: 98.4-99.9)				

PPA = Positive Percent Agreement, NPA = Negative Percent Agreement, CI = Confidence Interval

Of the Xpert MRSA/SA Blood Culture Assay runs on eligible specimens, 96.1% (764/795) were successful on the first attempt. The remaining 31runs gave indeterminate results on the first attempt (1 "INVALID", 22 "ERROR" and 8 "NO RESULT"). Thirty of the 31 indeterminate cases were retested; one specimen was not retested. Twenty-eight of the 30 indeterminate cases that were retested yielded valid results upon repeat assay. The overall rate of assay success was 99.6% (792/795).

Reproducibility Study

Reproducibility of the Xpert MRSA/SA Assay was evaluated at three sites using samples comprised of cultured material spiked into a simulated matrix. The samples were prepared at concentration levels representing high negative (below LoD), low positive (~1X LoD) and moderate positive (~2-3X LoD) for both MRSA and MSSA. Two different strains of MRSA were used. Negative panel members were also included and were comprised of *Staphylococcus epidermidis* spiked into a simulated matrix. A panel of 11 samples was tested on five different days by two different operators three times per day at three sites (11 samples x 2 operators x 5 days x 3 replicates per day x 3 sites). One lot of Xpert MRSA/SA reagents was included in the study. Xpert MRSA/SA Assays were performed according to the Xpert MRSA/SA Assay procedure. The rate of agreement for each panel member is presented in Table 5.5.

Table 5.5. Summary of Reproducibility Results – Agreement by Study Site/Instrument

Sample	Site 1/ GX Dx	Site 2/ Inf-80	Site 3/ Inf-48	% Total Agreement
MRSA-1 high neg (below LOD)	56.7% (17/30)	60.0% (18/30)	66.7% (20/30)	61.1% (55/90)
MRSA-1 low pos (~1X LOD)	100.0% (30/30)	100.0% (30/30)	100.0% (30/30)	100.0% (90/90)
MRSA-1 mod pos (~2-3X LOD)	100.0% (30/30)	100.0% (30/30)	100.0% (29/29)	100.0% (89/89)[a]
MRSA-2 high neg (below LOD)	43.3% (13/30)	53.3% (16/30)	70.0% (21/30)	55.6% (50/90)
MRSA-2 low pos (~1X LOD)	100.0% (30/30)	100.0% (30/30)	100.0% (30/30)	100.0% (90/90)
MRSA-2 mod pos (~2-3X LOD)	100.0% (30/30)	100.0% (30/30)	100.0% (30/30)	100.0% (90/90)
MSSA high neg (below LOD)	60.0% (18/30)	48.3% (14/29)	70.0% (21/30)	59.6% (53/89)[b]
MSSA low pos (~1X LOD)	96.7% (29/30)	100.0% (30/30)	96.7% (29/30)	97.8% (88/90)
MSSA mod pos (~2-3X LOD)	100.0% (30/30)	100.0% (30/30)	100.0% (30/30)	100.0% (90/90)
Negative-1	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)
Negative-2	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)

[a]One sample indeterminate after initial and retest.
[b]One sample mistakenly not run.

The reproducibility of the Xpert MRSA/SA Assay was also evaluated in terms of the fluorescence signal expressed in cycle threshold (Ct) values for each target detected. The mean, standard deviation (SD), and coefficient of variation (CV) between-sites, between-lots, between-days, and between-runs for each panel member are presented in Table 5.6.

Table 5.6. Summary of Reproducibility Data

Target	Sample	Conc	Agree/N	Agrmt (%)	Mean Ct	Between-Instrument		Between-Day		Between-Run[1]		Within-Run		Total	
						SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
spa	MRSA-1	high neg	55/90	61.1	35.6	0.18	0.5	0.21	0.6	0.00	0.0	0.95	2.7	0.99	2.8
	MRSA-1	low pos	90/90	100.0	32.8	0.27	0.8	0.00	0.0	0.00	0.0	0.62	1.9	0.67	2.1
	MRSA-1	mod pos	89/89	100.0	31.2	0.11	0.4	0.00	0.0	0.00	0.0	0.58	1.9	0.59	1.9
	MRSA-2	high neg	50/90	55.6	35.3	0.15	0.4	0.00	0.0	0.00	0.0	0.99	2.8	1.00	2.8
	MRSA-2	low pos	90/90	100.0	32.3	0.11	0.4	0.00	0.0	0.13	0.4	0.63	1.9	0.65	2.0
	MRSA-2	mod pos	90/90	100.0	30.7	0.00	0.0	0.00	0.0	0.00	0.0	0.55	1.8	0.55	1.8
	MSSA	high neg	53/89	59.6	36.3	0.00	0.0	0.00	0.0	0.00	0.0	1.26	3.5	1.26	3.5
	MSSA	low pos	88/90	97.8	33.5	0.07	0.2	0.18	0.5	0.00	0.0	0.89	2.7	0.91	2.7
	MSSA	mod pos	90/90	100.0	31.7	0.08	0.2	0.20	0.6	0.17	0.6	0.48	1.5	0.56	1.8
	NEG-1	Neg	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-2	Neg	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
mec	MRSA-1	high neg	55/90	61.1	35.8	0.00	0.0	0.36	1.0	0.00	0.0	0.83	2.3	0.91	2.5
	MRSA-1	low pos	90/90	100.0	33.4	0.12	0.4	0.19	0.6	0.00	0.0	0.55	1.6	0.59	1.8
	MRSA-1	mod pos	89/89	100.0	31.9	0.08	0.2	0.00	0.0	0.00	0.0	0.46	1.4	0.47	1.5
	MRSA-2	high neg	50/90	55.6	35.8	0.00	0.0	0.34	0.9	0.00	0.0	1.03	2.9	1.08	3.0
	MRSA-2	low pos	90/90	100.0	32.8	0.11	0.3	0.00	0.0	0.16	0.5	0.51	1.6	0.54	1.7
	MRSA-2	mod pos	90/90	100.0	31.5	0.00	0.0	0.16	0.5	0.00	0.0	0.49	1.5	0.51	1.6
	MSSA	high neg	53/89	59.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	MSSA	low pos	88/90	97.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	MSSA	mod pos	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-1	Neg	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-2	Neg	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SCC	MRSA-1	high neg	55/90	61.1	37.2	0.20	0.5	0.37	1.0	0.35	1.0	0.82	2.2	0.98	2.6
	MRSA-1	low pos	90/90	100.0	34.5	0.19	0.5	0.23	0.7	0.00	0.0	0.59	1.7	0.66	1.9
	MRSA-1	mod pos	89/89	100.0	33.0	0.16	0.5	0.00	0.0	0.00	0.0	0.45	1.4	0.48	1.5
	MRSA-2	high neg	50/90	55.6	36.8	0.23	0.6	0.24	0.6	0.10	0.3	1.00	2.7	1.06	2.9
	MRSA-2	low pos	90/90	100.0	33.7	0.11	0.3	0.00	0.0	0.26	0.8	0.57	1.7	0.64	1.9
	MRSA-2	mod pos	90/90	100.0	32.4	0.00	0.0	0.09	0.3	0.00	0.0	0.45	1.4	0.46	1.4
	MSSA	high neg	53/89	59.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	MSSA	low pos	88/90	97.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	MSSA	mod pos	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-1	Neg	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-2	Neg	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SPC	MRSA-1	high neg	55/90	61.1	32.7	0.00	0.0	0.00	0.0	0.20	0.6	0.65	2.0	0.68	2.1
	MRSA-1	low pos	90/90	100.0	33.0	0.00	0.0	0.16	0.5	0.10	0.3	0.61	1.8	0.63	1.9
	MRSA-1	mod pos	89/89	100.0	33.0	0.27	0.8	0.00	0.0	0.00	0.0	0.83	2.5	0.87	2.6
	MRSA-2	high neg	50/90	55.6	33.1	0.23	0.7	0.00	0.0	0.10	0.3	0.85	2.6	0.89	2.7
	MRSA-2	low pos	90/90	100.0	32.9	0.15	0.5	0.00	0.0	0.00	0.0	0.78	2.4	0.79	2.4
	MRSA-2	mod pos	90/90	100.0	32.8	0.00	0.0	0.23	0.7	0.00	0.0	0.66	2.0	0.70	2.1
	MSSA	high neg	53/89	59.6	32.8	0.18	0.5	0.15	0.5	0.00	0.0	0.74	2.2	0.77	2.4
	MSSA	low pos	88/90	97.8	32.9	0.00	0.0	0.00	0.0	0.00	0.0	0.72	2.2	0.72	2.2
	MSSA	mod pos	90/90	100.0	33.0	0.00	0.0	0.31	0.9	0.00	0.0	0.69	2.1	0.76	2.3
	NEG-1	Neg	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-2	Neg	90/90	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Agrmt=Agreement, Conc=concentration, CV=coefficient of variation, N/A=Not Applicable for negative samples, SD=standard deviation

Note: The variance estimate from some factors may be numerically negative, which can occur if the variability due to those factors is very small. When this occurs, the variability as measured with SD and CV is set to 0.

[1]A run is defined as the three samples per panel member run by one operator at one site on one day.

Instrument System Precision Study

An in-house precision study was conducted to compare the performance of the GeneXpert Dx, the Infinity-48 and the Infinity-80 Instrument Systems using samples comprised of cultured material spiked into a simulated matrix. The samples were prepared at concentration levels representing high negative (below LoD), low positive (~1X LoD) and moderate positive (~2-3X LoD) for both MRSA and MSSA. Two different strains of MRSA were used. Negative panel members were also included and were comprised of *Staphylococcus epidermidis* spiked into a

simulated matrix. A panel of 11 specimens was tested on 12 different days by two different operators four times per day per instrument (11 specimens x 2 operators x 12 days x 4 replicates per day x 3 instruments). One lot of Xpert MRSA/SA reagents was included in the study. Xpert MRSA/SA Assays were performed according to the Xpert MRSA/SA Assay procedure. The rate of agreement for each panel member is presented in Table 5.7.

Table 5.7: Summary of Precision Results – Agreement by Instrument

Sample	GX Dx	Inf-48	Inf-80	% Total Agreement
MRSA-1 high neg (below LOD)	50.0% (48/96)	51.6% (49/95)	35.4% (34/96)	45.6% (131/287)[a]
MRSA-1 low pos (~1X LOD)	96.9% (93/96)	99.0% (95/96)	99.0% (95/96)	98.3% (283/288)
MRSA-1 mod pos (~2-3X LOD)	100.0% (96/96)	100.0% (96/96)	99.0% (95/96)	99.7% (287/288)
MRSA-2 high neg (below LOD)	80.2% (77/96)	78.1% (75/96)	80.2% (77/96)	79.5% (229/288)
MRSA-2 low pos (~1X LOD)	100.0% (96/96)	100.0% (96/96)	100.0% (96/96)	100.0% (288/288)
MRSA-2 mod pos (~2-3X LOD)	100.0% (96/96)	100.0% (96/96)	99.0% (95/96)	99.7% (287/288)
MSSA high neg (below LOD)	76.0% (73/96)	71.9% (69/96)	81.3% (78/96)	76.4% (220/288)
MSSA low pos (~1X LOD)	96.9% (93/96)	99.0% (95/96)	100.0% (96/96)	98.6% (284/288)
MSSA mod pos (~2-3X LOD)	100.0% (96/96)	100.0% (96/96)	100.0% (96/96)	100.0% (288/288)
Negative-1	100.0% (96/96)	100.0% (96/96)	100.0% (96/96)	100.0% (288/288)
Negative-2	100.0% (96/96)	100.0% (96/96)	100.0% (96/96)	100.0% (288/288)

[a]One sample was indeterminate after initial and retest.

The precision study results were also evaluated in terms of the fluorescence signal expressed in Ct values for each target detected. The mean, standard deviation (SD), and coefficient of variation (CV) between-instruments, between-days, and between-runs for each panel member are presented in Table 5.8.

Table 5.8: Summary of Precision Data

Target	Sample	Conc	Agree/N	Agrmt (%)	Mean Ct	Between-Instrument		Between-Day		Between-Run[1]		Within-Run		Total	
						SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
spa	MRSA-1	high neg	131/287	45.6	34.4	0.00	0.0	0.00	0.0	0.00	0.0	1.09	3.2	1.09	3.2
	MRSA-1	low pos	283/288	98.3	32.9	0.02	0.1	0.16	0.5	0.00	0.0	0.78	2.4	0.80	2.4
	MRSA-1	mod pos	287/288	99.7	32.0	0.06	0.2	0.10	0.3	0.00	0.0	0.62	1.9	0.63	2.0
	MRSA-2	high neg	229/288	79.5	36.2	0.14	0.4	0.00	0.0	0.00	0.0	1.19	3.3	1.35	3.7
	MRSA-2	low pos	288/288	100.0	32.4	0.03	0.1	0.00	0.0	0.00	0.0	0.57	1.8	0.62	1.9
	MRSA-2	mod pos	287/288	99.7	31.1	0.12	0.4	0.00	0.0	0.00	0.0	0.49	1.6	0.51	1.7
	MSSA	high neg	220/288	76.4	36.4	0.21	0.6	0.00	0.0	0.00	0.0	1.36	3.7	1.59	4.4
	MSSA	low pos	284/288	98.6	33.8	0.09	0.3	0.18	0.5	0.00	0.0	0.87	2.6	0.90	2.7
	MSSA	mod pos	288/288	100.0	32.2	0.08	0.3	0.00	0.0	0.00	0.0	0.70	2.2	0.74	2.3
	NEG-1	Neg	288/288	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-2	Neg	288/288	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
mec	MRSA-1	high neg	131/287	45.6	34.5	0.00	0.0	0.11	0.3	0.00	0.0	0.86	2.5	0.87	2.5
	MRSA-1	low pos	283/288	98.3	33.4	0.07	0.2	0.14	0.4	0.00	0.0	0.61	1.8	0.63	1.9
	MRSA-1	mod pos	287/288	99.7	32.5	0.08	0.2	0.00	0.0	0.00	0.0	0.55	1.7	0.56	1.7
	MRSA-2	high neg	229/288	79.5	35.9	0.00	0.0	0.28	0.8	0.00	0.0	1.02	2.8	1.06	2.9
	MRSA-2	low pos	288/288	100.0	32.8	0.06	0.2	0.00	0.0	0.00	0.0	0.49	1.5	0.53	1.6
	MRSA-2	mod pos	287/288	99.7	31.5	0.14	0.5	0.05	0.2	0.00	0.0	0.45	1.4	0.47	1.5
	MSSA	high neg	220/288	76.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	MSSA	low pos	284/288	98.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	MSSA	mod pos	288/288	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-1	Neg	288/288	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-2	Neg	288/288	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SCC	MRSA-1	high neg	131/287	45.6	36.7	0.18	0.5	0.00	0.0	0.00	0.0	1.51	4.1	1.52	4.1
	MRSA-1	low pos	283/288	98.3	34.7	0.00	0.0	0.20	0.6	0.00	0.0	1.11	3.2	1.13	3.2
	MRSA-1	mod pos	287/288	99.7	33.7	0.12	0.3	0.00	0.0	0.00	0.0	0.78	2.3	0.78	2.3
	MRSA-2	high neg	229/288	79.5	37.3	0.00	0.0	0.32	0.8	0.00	0.0	1.03	2.8	1.17	3.1
	MRSA-2	low pos	288/288	100.0	34.2	0.02	0.1	0.00	0.0	0.00	0.0	0.44	1.3	0.50	1.5
	MRSA-2	mod pos	287/288	99.7	33.0	0.12	0.4	0.03	0.1	0.00	0.0	0.49	1.5	0.50	1.5
	MSSA	high neg	220/288	76.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	MSSA	low pos	284/288	98.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	MSSA	mod pos	288/288	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-1	Neg	288/288	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NEG-2	Neg	288/288	100.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SPC	MRSA-1	high neg	131/287	45.6	33.4	0.00	0.0	0.17	0.5	0.00	0.0	0.84	2.5	0.86	2.6
	MRSA-1	low pos	283/288	98.3	33.4	0.10	0.3	0.21	0.6	0.00	0.0	0.77	2.3	0.80	2.4
	MRSA-1	mod pos	287/288	99.7	33.4	0.08	0.2	0.15	0.5	0.00	0.0	0.72	2.2	0.74	2.2
	MRSA-2	high neg	229/288	79.5	33.4	0.00	0.0	0.00	0.0	0.00	0.0	0.82	2.4	0.82	2.4
	MRSA-2	low pos	288/288	100.0	33.4	0.02	0.1	0.00	0.0	0.00	0.0	0.73	2.2	0.77	2.3
	MRSA-2	mod pos	287/288	99.7	33.3	0.00	0.0	0.09	0.3	0.00	0.0	0.74	2.2	0.75	2.2
	MSSA	high neg	220/288	76.4	33.4	0.00	0.0	0.20	0.6	0.00	0.0	0.83	2.5	0.85	2.6
	MSSA	low pos	284/288	98.6	33.5	0.00	0.0	0.00	0.0	0.00	0.0	0.86	2.6	0.87	2.6
	MSSA	mod pos	288/288	100.0	33.1	0.11	0.3	0.00	0.0	0.00	0.0	0.75	2.2	0.77	2.3
	NEG-1	Neg	288/288	100.0	33.4	0.00	0.0	0.13	0.4	0.00	0.0	0.85	2.6	0.87	2.6
	NEG-2	Neg	288/288	100.0	33.5	0.00	0.0	0.02	0.1	0.00	0.0	0.84	2.5	0.84	2.5

Agrmt=Agreement, Conc=concentration, CV=coefficient of variation, N/A=Not Applicable for negative samples, SD=standard deviation

Note: The variance estimate from some factors may be numerically negative, which can occur if the variability due to those factors is very small. When this occurs, the variability as measured with SD and CV is set to 0.

[1]A run is defined as the four samples per panel member run by one operator at one site on one day.

Conclusions

The results of the nonclinical analytical and clinical performance studies summarized above demonstrate that the Xpert MRSA/SA Blood Culture Assay is substantially equivalent to the predicate devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

RAINER ZIERMANN, PH.D.
VICE PRESIDENT, CLINICAL AFFAIRS
CEPHEID
904 CARRIBEAN DRIVE
SUNNYVALE CA 94089

June 20, 2013

Re: K130894
Trade/Device Name: Xpert MRSA/SA Blood Culture Assay
Regulation Number: 21 CFR 866.1640
Regulation Name: Antimicrobial susceptibility test powder
Regulatory Class: II
Product Code: NQX
Dated: March 29, 2013
Received: April 02, 2013

Dear Dr. Ziermann:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Uwe Scherf -S for

Sally A. Hojvat, M.Sc., Ph.D.
Director, Division of Microbiology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

4.0 Indications for Use

Indications for Use Form

510(k) Number (if known): k130894

Device Name: Xpert® MRSA/SA Blood Culture Assay

Indications for Use:

The Cepheid Xpert® MRSA/SA Blood Culture Assay, performed on the GeneXpert® Instrument Systems, is a qualitative *in vitro* diagnostic test intended for the detection of *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) DNA directly from positive blood cultures. The assay utilizes automated real-time polymerase chain reaction (PCR) for the amplification of MRSA/SA specific DNA targets and fluorogenic target-specific hybridization probes for the real-time detection of the amplified DNA. The assay is performed directly on positive blood culture samples from BD BACTEC™ Plus Aerobic/F, BacT/ALERT® SA (Standard Aerobic) or VersaTREK REDOX 1® (aerobic) blood culture bottles that are determined by Gram stain as Gram Positive Cocci in Clusters (GPCC) or as Gram Positive Cocci in singles (GPC). The Xpert MRSA/SA Blood Culture Assay is indicated for use in conjunction with other laboratory tests, such as culture, and clinical data available to the clinician as an aid in the detection of MRSA/SA from positive blood cultures. Subculturing of positive blood cultures is necessary to recover organisms for susceptibility testing or for epidemiological typing. The Cepheid Xpert MRSA/SA Blood Culture Assay is not intended to monitor treatment for MRSA/SA infections.

Prescription Use ___X___ (Part 21 CFR 801 Subpart D)	AND/OR	Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

John Hobson -S
2013.06.18 14:48:57 -04'00'

Division Sign-Off
Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) k130894